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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: BENNEKER, et al.	:	Group Art Unit: 1612
Serial No: 08/872,023	:	Examiner: Chang, C.
Filed: June 10, 1997	:	Atty. Dkt.: 06854.0002
For: **4-Phenylpiperidine Compounds**	:	

DECLARATION UNDER 37 C.F.R. 1.132

I, Theodorus Hendricus A. Peters, do hereby declare as follows:

1. I am a co-inventor of the above-identified application.

2. I received a chemical laboratory engineering diploma (an "ing" diploma comparable to a bachelors degree) in 1984 from the technical school OLAN (Arnhem, The Netherlands). In 1989 I received a diploma (equivalent to a bachelors degree) in chemistry and in 1990 a general diploma (a "Drs." diploma comparable to a masters degree) in Chemistry, both from the University of Utrecht (Utrecht, The Netherlands). Subsequently in 1993 I completed my course work for a Ph.D.[1] in Chemistry, specialized in organic and organometallic chemistry, also at the University of Utrecht (Utrecht, The Netherlands).

3. I have been employed in the chemical research field since 1985 by several different employers including universities and private companies. In 1993 I joined Synthon BV, the assignee of the present application, as head of the Chemical Research and Development Department, and remain in this position to the present day.

4. I am familiar with the prosecution history of the present application, including the Office Action dated April 23, 1998. In order to further demonstrate the unobviousness of the present invention, I offer the following data on solubility and stability. Unless otherwise indicated, all data was determined/measured by me or by a subordinate under my direct supervision and control.

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[1] The defense of my thesis is expected to be done sometime next year after which the Ph.D. degree should be officially granted.

Solubility

The solubility of various paroxetine compounds was measured gravimetricly at 20°C by the following procedure. An exactly weighed amount (from about 50-200 mg) was stirred for at least one hour in a fixed amount of water (1 to 50 ml). When all the solid substance dissolved, an additional exactly weighed amount was added and stirred again for at least one hour. The addition and stirring was repeated whenever the substance fully dissolved. In the cases when a concentration of 1000 (or more) mg per ml was reached and there was still a clear solution (mesylate, besylate and tosylate) then the result is reported as "higher than 1000" mg/ml. When a suspension was observed after stirring, then the solid was filtered off, dried and weighed. The amount of compound soluble in the given volume of water was then calculated by the difference between the total added amount and the amount of the filtrate (maleate and acetate). In the cases of the fumarate and the tartrate, the solid was not able to be filtered off in a proper way. In these cases the solubilities are reported as "less than [the added amount]" per ml. The results are shown below:

Solubility of Paroxetine Compounds (mg per ml of water)	
paroxetine methane sulfonate (mesylate)	more than 1000
paroxetine benzene sulfonate (besylate)	more than 1000
paroxetine toluene sulfonate (tosylate)	more than 1000
paroxetine hydrochloride anhydrate	8.2*
paroxetine hydrochloride hemihydrate	4.9*
paroxetine maleate	7.0
paroxetine fumarate*	less than 7
paroxetine tartrate*	less than 7
paroxetine acetate	200

* published value
# novel comparison salt of paroxetine

The sulfonate salts of paroxetine which correspond to the present invention, exhibit over 5 times the solubility of the acetate salt and over 100 times the solubility of the other comparison

compounds. This dramatic increase in solubility exhibited by the sulfonate salts constitutes a significant and substantial improvement over the prior art paroxetine compounds (and over the novel, non-prior art, comparison compounds). The data shows that unlike other pharmaceutically acceptable salts which generally have a solubility of less than 10 mg/ml, the sulfonate salts have a solubility of greater than 1000 mg/ml. Such an increase in solubility by the use of a sulfonate salt was not predicted or suggested by any of the prior art teachings of which I am aware.

Stability

The solid state stability of various paroxetine compounds was measured using thermogravimetric analysis (TGA). TGA curves were produced using a Mettler Toledo TGA/SDTA851e in open aluminum oxide pans of 70 µl. The measurements were carried out with 15-20 mg samples under nitrogen with a flow rate of 70 ml per minute. The starting temperature was 25°C, heating at a rate of 10°C per minute and the measurements were stopped at 300°C. A blanc curve was recorded with an empty pan under the same conditions. This blanc curve was subtracted for each TGA. Between the measurements a calibration with the calibration weights in the module was performed. The TGA curves are set forth in Exhibits 1 and 2.

Exhibit 1 shows the thermal degradation of the following paroxetine compounds:

Inventive Compounds	Comparison Compounds
paroxetine methane sulfonate (mesylate)	paroxetine hydrochloride hemihydrate
paroxetine benzene sulfonate (besylate)	paroxetine free base
paroxetine toluene sulfonate (tosylate)	paroxetine maleate
paroxetine *p*-chlorobenzene sulfonate (*p*-chlorobesylate)	paroxetine fumarate#
	paroxetine tartrate#
	paroxetine acetate

novel comparison paroxetine salt

The Y-axis of the plot shown in Exhibit 1 indicates the amount of paroxetine compound while the X-axis indicates both the temperature and duration of the test. It should be noted that the curves have been separated for clarity. That is, the curves do not start at a common point on

the Y axis. The change in weight amount of each paroxetine compound relative to its own starting point can thus be clearly seen. The bar on the Y-axis provides a frame of reference by indicating the distance along the Y-axis that corresponds to a 10 mg change in the amount of the compound.

The stability of a pharmaceutical compound is a factor in determining its commercial or practical viability. The more rapidly (shorter time or lower temperature) that a compound degrades, the less stable the compound. Thus, the flatter the TGA curve (smaller ΔY), the lower the amount of degradation and the more stable the compound. Conversely, the greater the drop, the less stable the compound.

The TGA curves in Exhibit 1 show that the sulfonate salts of paroxetine have good to excellent stability and are more stable than any of the comparison compounds. In particular, the mesylate, besylate and tosylate salts are very stable, while the *p*-chlorobesylate salt is slightly more stable than the hydrochloride hemihydrate salt. Although both the hydrochloride hemihydrate and the *p*-chlorobesylate loose water at around 130 °C, the loosing of water for the hydrochloride is shaper than for the *p*-chlorobesylate. But, at higher temperatures the hydrochloride hemihydrate shows a bit more degradation than the *p*-chlorobesylate. Accordingly, the stability of these compounds is given as:

- mesylate > besylate > tosylate >>> *p*-chlorobesylate > hydrochloride hemihydrate > fumarate > maleate > free base > tartrate >> acetate.

This result is surprising in that the sulfonate salts are more stable, and in some cases greatly more stable, than the commercially available form of paroxetine (the hydrochloride hemihydrate).

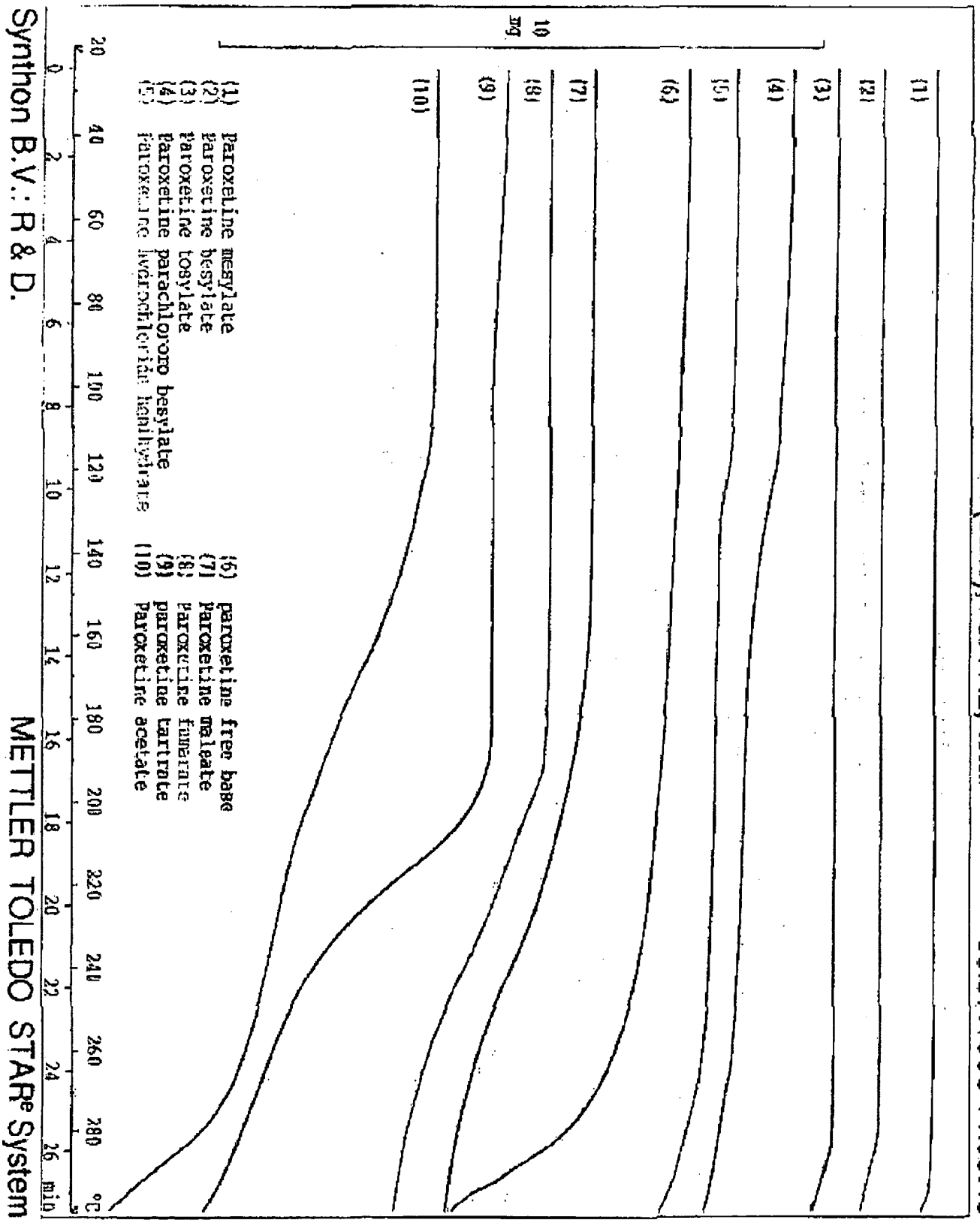
Exhibit 2 shows the magnified TGA curves for the mesylate, the free base (fresh and stored), the maleate, and the acetate forms, with each curve starting at the same point. It is apparent that degradation for the paroxetine free base (fresh and stored) and the acetate salt has begun by 60°C, and that by 120°C all of the comparison compounds including the maleate are clearly degrading and unstable. The mesylate compound, in contrast, does not begin to degrade until after 260°C.

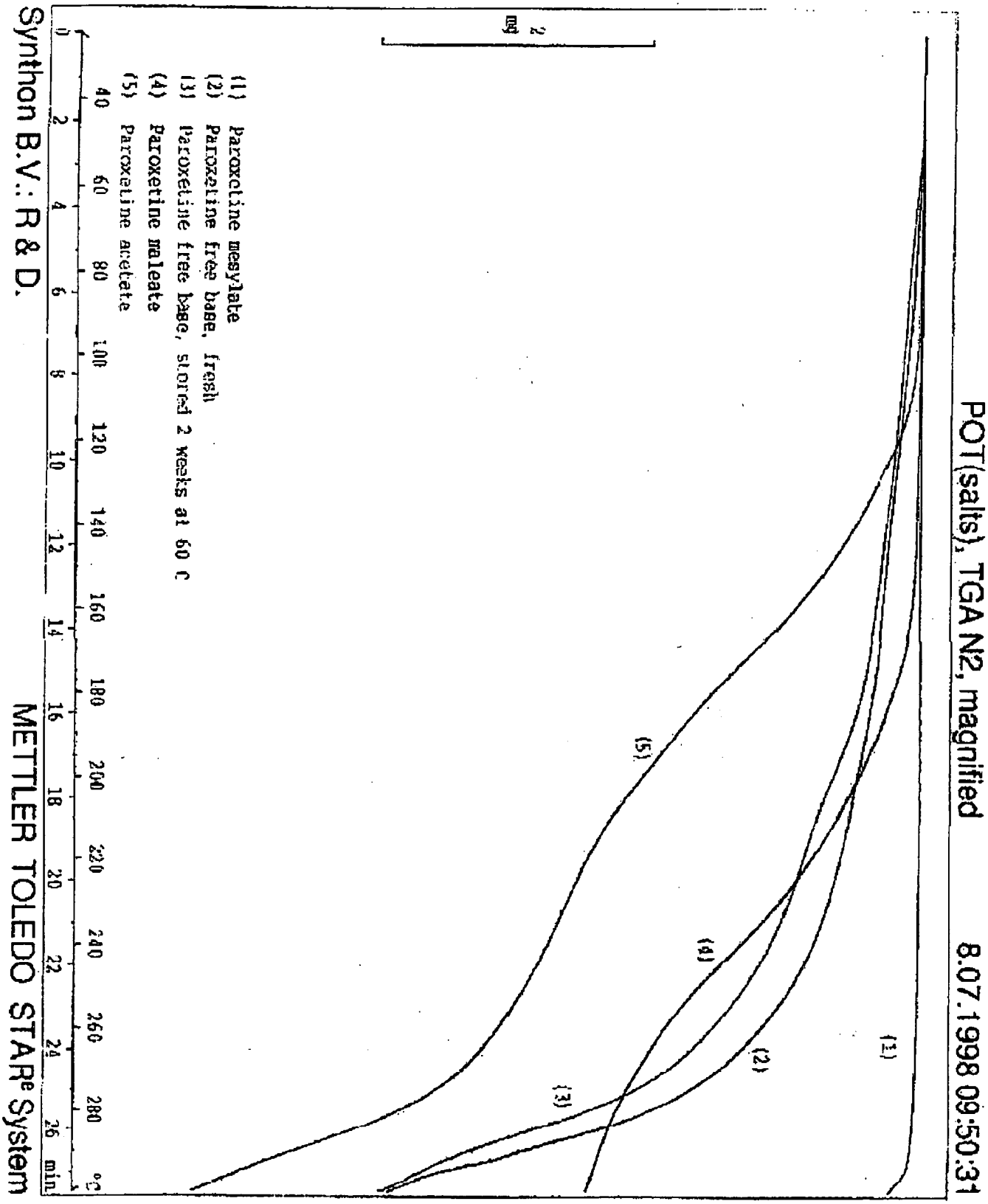
Accordingly, the sulfonate salts demonstrated high and improved stability and are thus suitable for use in pharmaceutical compositions.

5. I further declare that the above statements are true and that all statements made upon information and belief are believed to be true and furthermore that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and may jeopardize the validity of the application or any patent issuing thereon.

22/9/2004
Date

Theodorus Hendricus A. Peters


POT(salts), TGA N2, total
03.07.1998 14:06:46
10 mg
(1) Paroxetine mesylate
(2) Paroxetine besylate
(3) Paroxetine tosylate
(4) Paroxetine parachloroom besylate
(5) Paroxetine hydrochloride hemihydrate
(6) paroxetine free base
(7) Paroxetine maleate
(8) Paroxetine fumarate
(9) paroxetine tartrate
(10) Paroxetine acetate
Synthon B.V.: R & D.
METTLER TOLEDO STARe System
20 40 60 80 100 120 140 160 180 200 220 240 260 280 °C
0 2 4 6 8 10 12 14 16 18 20 22 24 26 min


POT(salts), TGA N2, magnified
8.07.1998 09:50:31
mg 2
(1) Paroxetine mesylate
(2) Paroxetine free base, fresh
(3) Paroxetine free base, stored 2 weeks at 60 C
(4) Paroxetine maleate
(5) Paroxetine acetate
(1)
(2)
(3)
(4)
(5)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 min
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 °C
Synthon B.V.: R & D.
METTLER TOLEDO STARe System